Docket No.: 511582001100
(PATENT)

**IN THE UNITED STATES PATENT AND TRADEMARK OFFICE**

In re Patent Application of:
Daniel E. H. AFAR, et al.

Application No.: 09/547,789

Art Unit: 1642

Filed: April 12, 2000

Examiner: Anne L. Holleran

For: NOVEL 13-TRANSMEMBRANE PROTEIN EXPRESSED IN PROSTATE CANCER

**DECLARATION OF PIA M. CHALLITA-EID**
**UNDER 37 C.F.R. § 1.132**

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Dear Sir:

I, Pia M. Challita-Eid, declare as follows:

1. I have a Ph.D. in Microbiology from University of Southern California, did post doctoral work at University of California at Los Angeles, and was a faculty member at the University of Rochester. I have been practicing in the field of molecular biology for over 10 years. At Agensys, I am the Group Leader of Gene Discovery. In my position at Agensys, I have responsibility for evaluating the levels of expression of various genes in tissues. A copy of my *curriculum vitae* is enclosed as Exhibit A.

2. Although I did not myself conduct them, I have direct personal familiarity with the conduct of the experiments described below.

3. We tested the levels of expression of 24P4C12 protein by immunohistochemistry in normal and tumor specimens of ovary. Formalin fixed, paraffin wax-embedded tissues were cut into 4 micron sections and mounted on glass slides. The sections were de-waxed, rehydrated and treated with antigen retrieval solution (0.1M Tris, pH 10) at high temperature. Sections were then incubated in polyclonal rabbit anti-24P4C12 antibody for 3 hours. The slides were washed three times in buffer and further incubated with DAKO EnVision+™ peroxidase-conjugated goat anti-rabbit immunoglobulin secondary antibody (DAKO Corporation, Carpentaria, CA) for 1 hour. The sections were then washed in buffer, developed using the DAB kit (SIGMA Chemicals), counterstained using hematoxylin, and analyzed by bright field microscopy. Positive stain shows brown, and the tissue which does not contain antigen immunoreactive with the 24P4C12 antibody stains blue. As shown in Exhibit B, normal ovary showed no expression of 24P4C12 (panel A) whereas the ovarian cancer specimen showed strong expression of 24P4C12 in the tumor cells (panel B). Expression of 24P4C12 was detected both within the cytoplasm of the tumor cells and on the cell surface indicating that 24P4C12 is membrane associated in ovarian cancer.

4. We also used the same antibodies and the same staining system set forth in the previous paragraph to monitor protein expression in prostate cancer. As described in the previous paragraph, formalin fixed, paraffin wax-embedded tissues were cut into 4 micron sections and mounted on glass slides, de-waxed, rehydrated and treated with antigen retrieval solution at high temperature. The same antibody detection system as described above was employed; therefore, a brown stain indicates the presence of the antigen. In addition, controls were run where a peptide derived from SEQ ID NO: 2 which binds the antibody was included; as expected, this blocked the labeling of the protein in the sample by the antibodies. As shown in Exhibits C and D, the

distribution of protein in normal vs. prostate cancer operates as a clear diagnostic. In the cancer tissue (Exhibit C), the tissue has no structure and is just a disorganized mass. However, in normal tissue, shown in Exhibit D, structural features of the tissue can be discerned. Thus, the contrast in pattern by immunohistochemistry permits the detection of cancer tissue in prostate.

5. We also tested a monoclonal antibody immunoreactive with 24P4C12 *in vivo* for an indication of its ability to retard the growth of human prostate xenographs. Exhibit E shows the results of this experiment. In this experiment, human prostate cancer LAPC-9AD was implanted subcutaneously in SCID mice (2,000,000 cells per mouse). In the controls, either phosphate buffered saline or an antibody raised to KLH were administered at the same levels as a monoclonal antibody immunoreactive with 24P4C12. The antibody was dosed intraperitoneally twice a week at 500 μg/mouse for a total of nine doses. As shown in the figures, in the controls, by day 30 the mean tumor volume had greatly increased; both the rate of increase and the level reached by day 30 were diminished by administering the antibody.

6. Although the Office appears to take the position that there is no correlation between levels of mRNA and the corresponding encoded protein in a reliable fashion, I can affirm that measurements of mRNA levels are routinely used by the skilled practitioners in this field as indices of gene expression, and indicate the probability of overexpression of the protein. In view of this common practice, I believe that results obtained by measuring mRNA levels, while not exhibiting 100% correlation, are indicative of high levels of protein expression. Accordingly, we tested a wide variety of cancer specimens using mRNA as a guide. First strand cDNA was prepared from a panel of ovary patient cancer specimens, bladder cancer specimens, uterus patient cancer specimens, and cervical patient cancer specimens. Normalization was performed by PCR using primers to actin.

Semi-quantitative PCR, using primers to 24P4C12, was performed at 26 and 30 cycles of amplification. Samples were run on an agarose gel, and PCR products were quantitated using the AlphaImager software. Expression was recorded as absent, low, medium or strong. The results are shown in Exhibit F where increasing levels of expression are indicated by increasing darkness of the rectangle indicating the results. Results show expression of 24P4C12 in the majority of all patient cancer specimens tested, 75% of ovary patient cancer specimens, 61% of bladder cancer patient specimens, 83.3% of uterus patient cancer specimens, and 86% of cervical cancer specimens.

7. In my expert opinion, the results above clearly show that:

(i) 24P4C12 protein is produced in ovarian cancer, but not in normal ovary tissue and can be detected by immunochemistry.

(ii) The presence of malignancy can be shown in prostate cancer by using antibody staining to show disorganization of the tissue in the presence of cancer.

(iii) Antibodies against 24P4C12 protein can control the growth of prostate cancer in an animal model

(iv) As a general matter, the level of expression of 24P4C12 is higher in cancer tissue than in normal tissue. This protein is apparently not expressed in normal ovary, normal uterus or normal bladder and is detectably or strongly expressed in a multiplicity of cancers associated with these organs. The cervix data indicate that strong or medium expression is found only in cancerous cervix tissue.

8. In view of these showings, it is apparent that 24P4C12 protein, or variants thereof which can be used to elicit the production of antibodies immunoreactive with 24P4C12 protein, are useful in detecting the presence of cancer as well as in therapeutic approaches to treatment.

Application No.: 09/547,789 Docket No.: 511582001100

I declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further, that these statements are made with the knowledge that willful, false statements and the like so made are punishable by fine or imprisonment or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

Executed at SANTA MONICA (city), CA (state), on 10 (day) March 2004.

Pia M. Challita-Eid

*Curriculum Vitae*

PIA M. CHALLITA-EID, PH.D

## Personal information

Home Address: 4229 Colbath Avenue
Sherman Oaks, CA 91423
Phone: (626) 233-9434
Work Address: University of Rochester
Cancer Center
601 Elmwood Avenue, Box #704
Rochester, NY 14642
Email address: *eid@frontiernet.net*
Date of Birth: June 17, 1966
Marital status: Married to Emile R. Eid

## Education:

B.S. Biology — American University of Beirut-Lebanon
1984-1987

M.S. Microbiology — American University of Beirut-Lebanon
1987-1989

Ph.D. Microbiology — University of Southern California
Department of Microbiology
January 1990 - June 1994
Sponsor: Donald B. Kohn, M.D., Associate, Professor
Departments of Pediatrics and Microbiology
Division of Research Immunology and Bone Marrow Transplantation
Childrens Hospital of Los Angeles
University of Southern California, California
USA

Postdoctoral fellowship — University of California Los Angeles
Department of Hematology-Oncology
September 1994 - December 1995

Sponsor: Joseph D. Rosenblatt, M.D., Assistant Professor
School of Medicine
Department of Hematology-Oncology
University of California, Los Angeles, California

## Appointments:

| | |
|---|---|
| Senior Instructor | University of Rochester<br>Cancer Center<br>Department of Oncology<br>January 1996- June 1998 |
| Assistant Professor in Medicine, Microbiology & Immunology | University of Rochester<br>Cancer Center<br>Hematology/Oncology Unit<br>July 1998- Present |

## Languages:

Fluent in English, French and Arabic.

## Students and Technicians Mentored:

1. Skelton Diane, Research Associate, 1992-1994.
2. El-Khoueiry Anthony, Undergraduate student, Summer 1992 and 1993. Currently resident in internal medicine at USC.
3. Poles Tina, Research Associate, 1996-1998.
4. Mosammaparast Nima, Undergraduate student, June 1996 - September 1997. Currently enrolled in Medical School.
5. Zoric Bojan, Undergraduate student, June 1997-June 1998. Currently enrolled in Medical School.
6. Rimel BJ, Research Associate, June 1998-June 1999.
7. Vicki Houseknecht, Research Associate, June 1999 - present.
8. Facciponte John, Graduate student in the Microbiology and Immunology Department at the University of Rochester, January 1998 - present.
9. Kyung Yi, Graduate Student in Microbiology, January 1999 - present.
10. Anagha Joshi, Post-doctoral fellow, October 1999 - present.

## Patents:

1) "Retroviral Vectors for Expression in Embryonic Cells", reference number 08/361,112 filed December 1994.
2) "Chimeric Proteins for the Stimulation of a Tumor-Specific Immune Response", application in progress.

## Invited Presentations:

October 1994 "Retroviral Vector Expression in Murine Stem Cells". Department of Hematology-Oncology, UCLA Gene Therapy Program, Los Angeles, California.

October 1997 "Antibody Fusion Proteins for the Specific Recruitment and Activation of an Anti-Tumor immune Response". Childrens Hospital of Los Angeles, Los Angeles, California.

February 1998 Regional Cancer Center Consortium for Biological Therapy. Roswell Park Cancer Institute, Buffalo, New York.

July 1998 American Cyanamid Company. Lederle-Praxis Biologicals Division, Rochester, New York.

October 1999 "Monoclonal Antibody Technology in the Era of Genetic Engineering" Brazilian Meeting on Biosafety and Transgenic Products, Rio De Janeiro, Brazil.

June 1999 "Breast Cancer Research in the Era of Genetic Engineering", Breast Cancer Coalition of Rochester, Rochester, NY.

## Awards:

**Graduate Student Research Forum Award.** Silencing of retroviral vectors after transduction of hematopoietic stem cells is associated with methylation. Graduate Student Research Forum Poster Session. USC Medical School, Los Angeles, California, 1993.

**Presidential Award.** Society of Biological Therapy, Pasadena, California, October 1997.

**Merit Award.** American Society of Clinical Oncology, California, May 1998.

## Grants/Funds:

1) Jonsson Cancer Center Foundation/UCLA
Fellowship Seed Grant
Title: "Antigen Processing in Human Neural Crest Tumors"
Effective Dates: 11/1/95-10/31/96

Amount: $27,707

2) Rochester Area Foundation
Lucille B. Kesel Fund for the Advancenent of Cancer Research
Title: "Antibody Fusion Proteins for Eradication of Minimal Residual Disease"
Effective Dates: 1/1/98-12/31/98
Amount: $8,000

3) University of Rochester Cancer Center
Interim and Pilot Project Funding
P.I.: Joseph D. Rosenblatt, M.D.
Co-P.I.: Pia M. Challita-Eid, Ph.D.
Title: "Antibody Fusion Proteins for the Therapy of Cancer".
Effective Dates: 1/1/98-12/31/98
Amount: $25,000

4) Sinsheimer Scholar Award
Title: "Genetically-Engineered Chemokine Antibody Fusion Proteins for Breast and Ovarian Cancer Therapy"
Effective Dates: 7/1/98-6/30/01
Amount: $40,000/year

5) NIH/NCI
P.I.: Joseph D. Rosenblatt, M.D.
Co-P.I.: Pia M. Challita-Eid, Ph.D.
Title: "Recruitment and Activation of an Anti-tumor Response using Antibody-Fusion Proteins"
Effective Dates: 12/1/98-11/30/03
Amount: $191,046/year

6) NIH/NCI - Rapid Access to Intervention Development (RAID)
Title: "Preclinical Development of a B7.1 Anti-HER2/neu Antibody Fusion Protein"
Effective Date: Approved April, 1999
Amount: Not applicable

7) ACS Institutional grant
Title: "Chemokine Directed Targeting of Cytotoxic TALL-104 Cells"
Effective Dates: 9/1/99-8/30/00
Amount: $8,000

8) Breast Cancer Coalition of Rochester
Title: "Breast Cancer Research"
Date: 9/99
Amount: $1,000

## Publications:


Gersuk GM, Westermark B, Mohabeer AJ, **Challita PM**, Pattamakom S, and Pattengale, PK. Inhibition of human natural killer cell activity by platelet- derived growth factor (PDGF). III. Membrane binding studies and differential biological effects of recombinant PDGF isoforms. *Scand J Immunol* 33: 521-532, 1991.

Gersuk GM, Carmel R, **Challita PM**, Rabinowitz AP, and Pattengale PK. Quantitative and functional studies of impaired natural killer (NK) cells in patients with myelofibrosis, essential thrombocytopenis, and polycythemia vera. I. A potential role for platelet-derived growth factor in defective NK cytotoxicity. *Nat Immun* 12: 136-151, 1993.

**Challita PM**, and Kohn DB. Lack of expression from a retroviral vector in murine hematopoietic stem cells is associated with methylation *in vivo*. *Proc Natl Acad Sci (USA)* 91: 2567-2571, 1994.

Krall W, **Challita PM**, Perlmutter L, Skelton D, and Kohn DB. Cells expressing human glucocerebrosidase from a retroviral vector repopulate macrophages and central nervous system microglia after murine bone marrow transplantation. *Blood* 83: 2737-2748, 1994.

**Challita PM**, Skelton D, Yu XJ, El-Khoueiry A, Yu X-J, Weinberg KI, and Kohn DB. Multiple modifications in *cis* elements of the long terminal repeat of retroviral vectors leads to increased expression and decreased DNA methylation in embryonic carcinoma cells. *J Virol* 69: 748, 1995.

Ucar K, Seeger RC, **Challita PM**,Watanabe CT, Yen TL, Morgan JP, Amado R, Chou E, McCallister T, Barber JR, Jolly DJ, Reynolds P, Gangavalli R, and Rosenblatt JD. Sustained cytokine production and immunophenotypic changes in human neuroblastoma cell lines transduced with a human gamma interferon vector. *Cancer Gene Therapy* 2: 171, 1995.

Lu Y, Planelles V, Palaniappan C, Li X, **Challita-Eid PM**, Amado R, Stephens D, Kohn DB, Bakker A, Day B, Bambara RA, and Rosenblatt JD. Inhibition of HIV-1 replication using a mutated tRNALys3 primer. *J Biol Chem* 272: 14523, 1997.

**Challita-Eid PM**, Penichet ML, Shin SU, Poles T, Mosammaparast N, Mahmood K, Slamon DJ, Morrison SL, and Rosenblatt JD. A B7.1-antibody fusion protein retains antibody specificity and ability to activate*via* the T cell costimulatory pathway. *J Immunol* 160: 3419-3426, 1998.

**Challita-Eid PM**, Abboud CN, Morrison SL, Penichet ML, Rosell KE, Poles T, Hilchey SP, Planelles V, and Rosenblatt JD. A RANTES- antibody fusion protein retains antigen specificity and chemokine function. *J Immunology* 161: 3729, 1998.

Challita-Eid PM, Rosenblatt JD, Day B, Rimel BJ and Planelles V. Inhibition of HIV-1 infection with a RANTES.IgG3 fusion protein. *AIDS Research and Human Retroviruses* 14:1617, 1998.

Mahmood K, Federoff HJ, **Challita-Eid PM**, Day B, Haltman M, Atkinson M, Planelles V, and Rosenblatt JD. Eradication of pre-established lymphoma using HSV amplicon vectors. *Blood* 93: 643, 1999

Penichet ML, Challita-Eid PM, Shin S-U, Sampogna S, Rosenblatt JD, and Morrison SL. Establishment of human HER2/neu expressing tumors. *Laboratory Animal Science* 49: 179-88, 1999.

Penichet ML, Dela Cruz JS, **Challita-Eid PM**, Rosenblatt JD, and Morrison SL. A Murine B cell lymphoma expressing human HER2/neu undergoes spontaneous tumor regression and elicits anti-tumor immunity. *Manuscript submitted.*

Hilchey SP, Rosebrough SF, Morrison SL, Rosenblatt JD, and **Challita-Eid PM.** Specific targeting and stimulation of in vivo anti-tumor response using a B7.1 T-cell costimulatory antibody fusion protein. *Manuscript in preparation.*

## Selected Abstracts and Presentations:

Challita PM, El-Khoueiry AB, and Kohn DB. Silencing of retroviral vectors after transduction of murine hematopoietic stem cells is associated with methylation. *Blood* 80 (10 Suppl. 1): 168a, 1992.

Challita PM, Cook C, Sender LS, and Kohn DB. Novel retroviral vectors for consistent expression after transduction into hematopoietic stem cells. Keystone Symposium on Gene Therapy, Keystone, Colorado, 1993.

Challita PM. Retroviral vector expression in murine stem cells. Presentation. Division of Hematology-Oncology, University of California Los Angeles, October, 1994.

Challita PM, Shin S-U, Penichet M, Mahmood K, Poles TM, Rosell KE, Abboud CN, Morrison SL, Rosenblatt JD. Novel Antibody Fusion Proteins for the Stimulation of a Tumor-Specific Immune Response. Keystone Symposium on Cellular Immunology and Immunotherapy of Cancer, Copper Mountain, Colorado, January 1997.

Penichet ML, Challita PM, Shin S-U, Slamon DJ, Rosenblatt JD, and Morrison SL. In vivo properties of two human her2/neu expressing murine cell lines in immunocompetent mice. Mutlidisciplinary Approaches to Cancer Immunotherapy, Bethesda, Maryland, June 1997.

**Challita PM**, Abboud CN, Rosell KE, Penichet ML, Poles T, Mahmood K, Morrison SL, and Rosenblatt JD. Characterization of a RANTES-antibody fusion protein for cancer immunotherapy. Mutlidisciplinary Approaches to Cancer Immunotherapy, Bethesda, Maryland, June 1997.

Horwitz S, Rosenblatt JD, Mosammaparast N, Poles T, Abboud CN, and **Challita PM**. Gene-modified EL4 cells expressing the chemokine RANTES protects from tumor growth and stimulates an anti-tumor cytotoxic T-lymphocyte response *in vivo*. Mutlidisciplinary Approaches to Cancer Immunotherapy, Bethesda, Maryland, June 1997.

**Challita-Eid PM**, Morrison SL, Penichet ML, Rosenblatt JD. Antibody-T cell costimulatory ligand fusion protein for the stimulation of a specific anti-tumor immune response. American Society of Hematology, San Diego, California, December 1997.

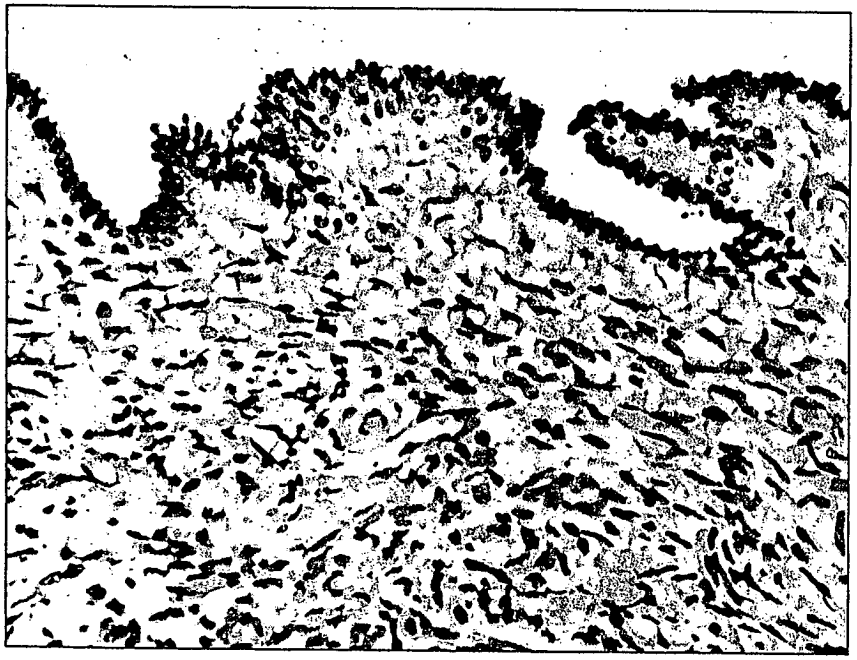
**Challita-Eid PM**, Abboud CN, Penichet ML, Rosell KE, Morrison SL, Rosenblatt JD. Antibody fusion proteins for the recruitment and activation of an anti-tumor immune response. American Association for Cancer Research. New Orleans, Louisiana, March 1998.

**Challita-Eid PM**, Hilchey Shannon P., and Rosenblatt Joseph D. An anti-HER2/neu RANTES fusion protein induces effector cell infiltration to the site of HER2/neu expressing tumors. AACR/NCI/EORTC Molecular Targets and Cancer Therapeutics, Washington DC, November 1999.

Facciponte JG, Rosenblatt JD, H.J.Federoff HJ, **Challita-Eid PM**. Herpes simplex virus (HSV) amplicon-mediated gene transfer of tumor associated antigens into bone marrow derived dendritic cells. Keystone Symposium on Cellular Immunity and Immunotherapy of Cancer, Santa Fe, New Mexico, January 2000.

# 24P4C12 Protein Expression is Detected in Ovarian Cancer but not in Normal Ovary

Normal ovary



papillary serous adenocarcinoma of ovary, Grade 2

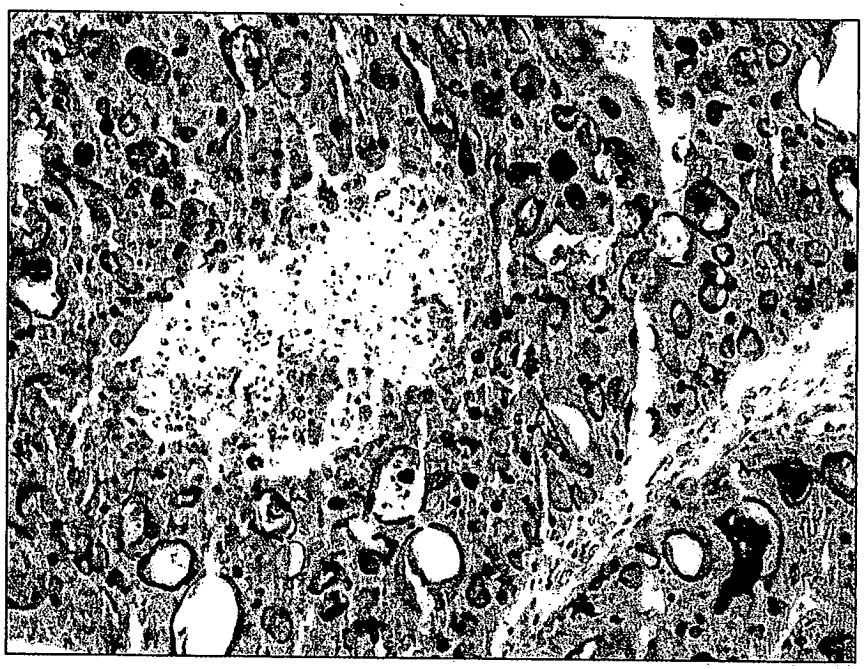
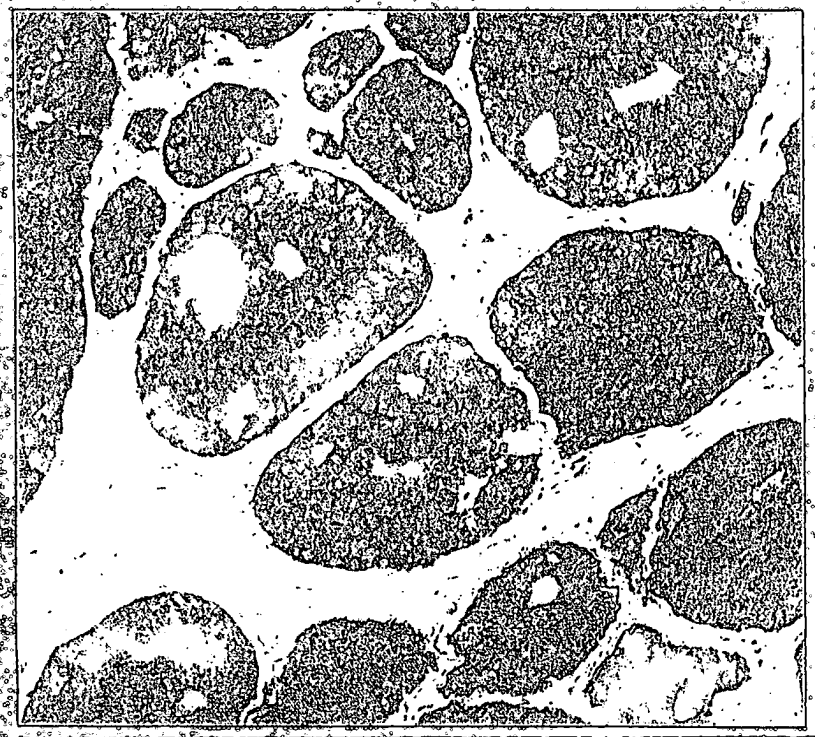
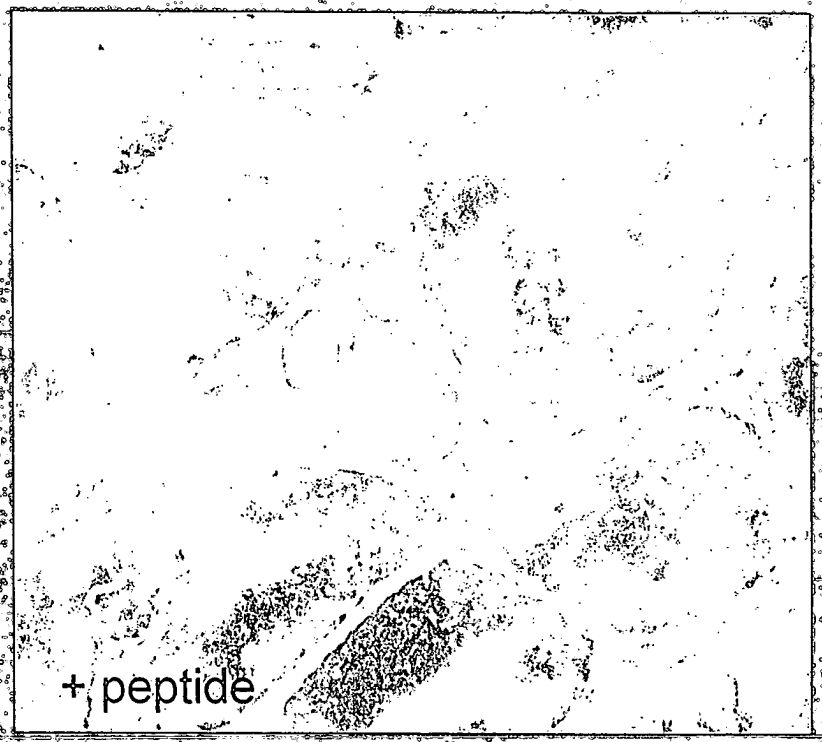


Exhibit B

# Exhibit XX: 24P4C12 Protein Expression in Prostate Cancer (frozen section, acetone fixed)





# Exhibit XX: 24P4C12 Protein Expression in Prostate NAT (frozen section, acetone fixed)

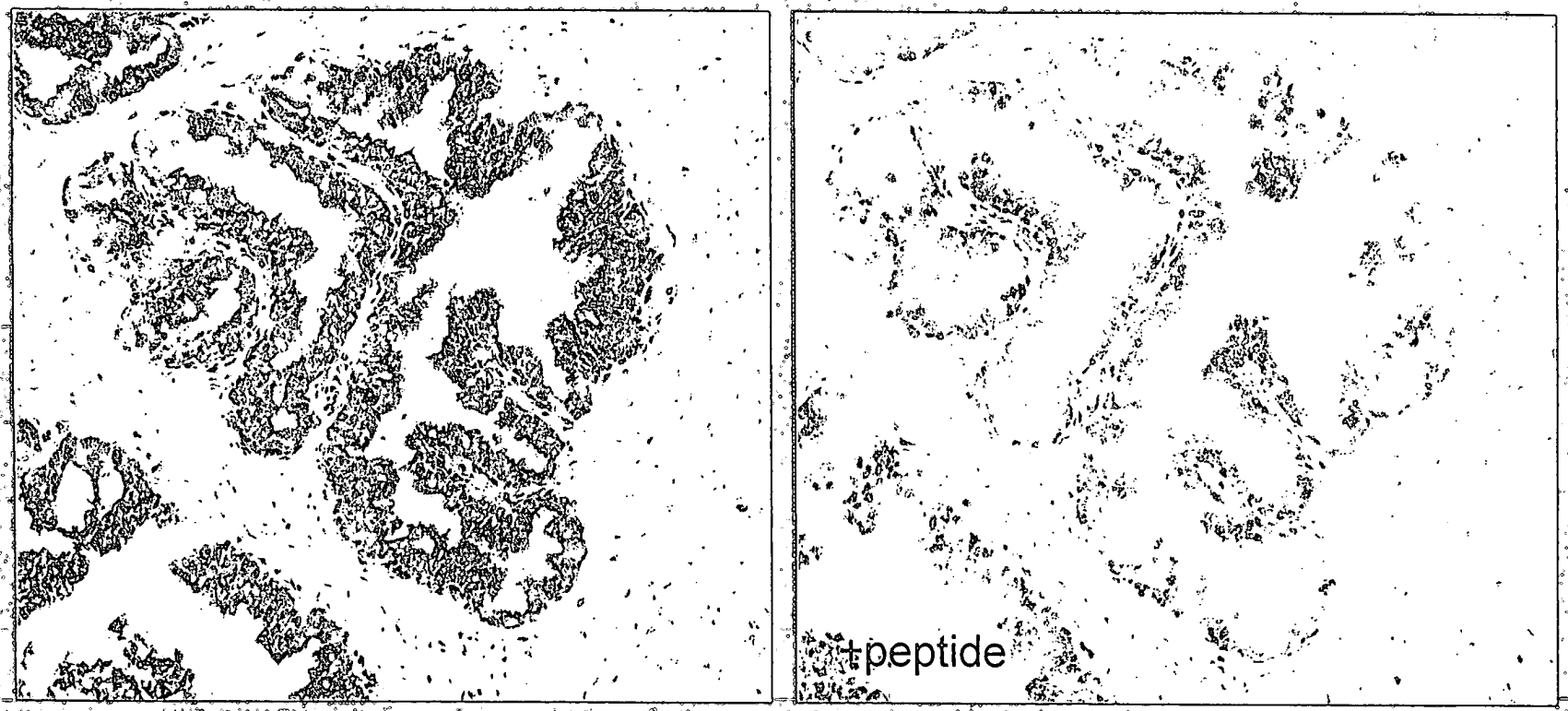



Exhibit D

# Exhibit XX: 24P4C12 MAb Retards the Growth of Human Prostate Cancer LAPC 9AD Xenograft in Mice

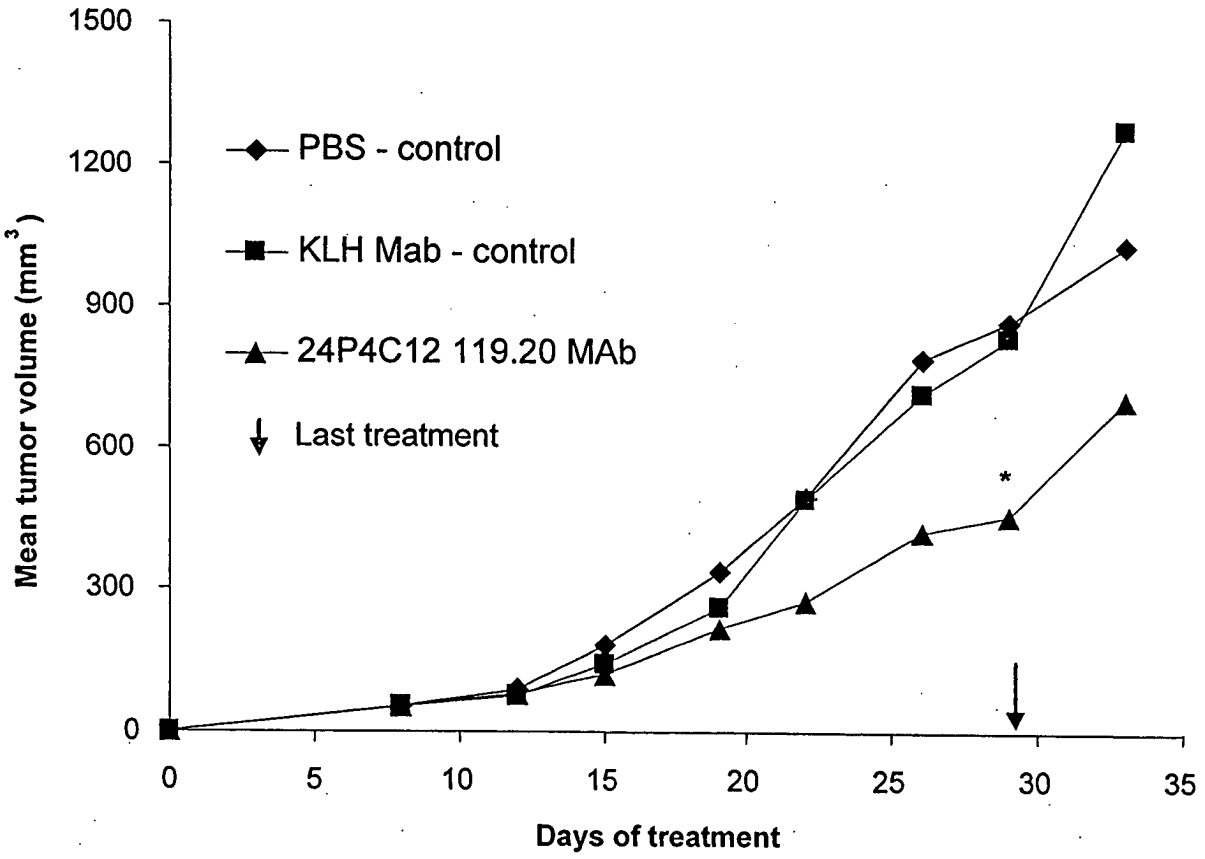



Exhibit E

♦ **Human prostate cancer LAPC 9AD was implanted s.c. in SCID mice (2 million cells per mouse). PBS or antibody treatment of either 24P4C12 119.20 Mab or KLH control Mab was started on the same day. Antibody was dosed ip twice a week at 500 µg/mouse for a total of 9 doses**

***24P4C12 MAb-treated mice vs. control mice on day 29: P<0.05 by Mann-Whitney U test.**

# Exhibit XX: 24P4C12 RNA Expression in Patient Cancer Specimens

## Ovary

| Sample # | Diagnosis | Grade | 24P4C12 |
|---|---|---|---|
| 1 | Normal Ovary | | |
| 2 | Serous CA | 3 | |
| 3 | Mucinous CystadenoCA | | |
| 4 | Mucinous CystadenoCA | | |
| 5 | Mucinous CystadenoCA | 2 | |
| 6 | Granulosa | Figo Ia1 | |
| 7 | Papillary serous CA | 3 | |
| 8 | Endometrioid AdenoCA | 2 | |
| 9 | Papillary serous CA | 3 | |
| 10 | ND | | |
| 11 | Squamous | 3 | |
| 12 | Adeno CA Met to Omentum | | |
| 13 | Papillary serous CA | Figo III | |
| 14 | Endometrioid AdenoCA | | |
| 15 | Met to falloplan tube | | |
| 16 | Met to Intestine | Undiff. | |
| 17 | ND | | |
| 18 | Met to Intestine | | |
| 19 | Met to Intestine | | |
| 20 | Met to Intestine | | |
| 21 | Met to Intestine | | |
| 22 | Met to Intestine | | |
| 23 | Endometrioid AdenoCA | | |
| 24 | Endometrioid CA | Mod diff | |
| 25 | Papillary serous met | | |
| 26 | Clear cell CA | Grade 1 | |
| 27 | Papillary serous met to omentum | | |
| 28 | Epithelial neoplasm | poorly diff | |
| 29 | Endometrioid CA | Grade 2 | |
| 30 | AdenoCA | poorly diff | |
| 31 | Sertoli Leydig | | |
| 32 | ND | | |
| 33 | Small cell carcinoma | Undiff. | |
| 34 | Papillary Serous CA | | |
| 35 | Endometrioid Adenocarcinoma | | |
| 36 | Papillary Serous Adenocarcinoma | | |
| 37 | Mucinous Intraglandular CA | | |
| 38 | AdenoCA mixed endometrioid & papillary | | |
| 39 | Papillary serous CA | poorly diff | |
| 40 | Papillary serous CA | mod diff | |
| 41 | Papillary serous CA | Grade IIIc | |
| 42 | Serous cystadenocarcinoma | Grade 1 | |
| 43 | Yolk sac tumor | Stage IIC | |
| 44 | Granulosa | | |
| 45 | AdenoCA | Grade 2 | |

## Uterus

| Sample # | Diagnosis | Grade | 24P4C12 |
|---|---|---|---|
| 1 | Normal Uterus | | |
| 2 | AdenoCA | Well diff. | |
| 3 | AdenoCA | G2 | |
| 4 | AdenoCA | G1 | |
| 5 | Stromal sarcoma | High grade | |
| 6 | AdenoCA | G2 | |
| 7 | AdenoCA | G1 | |
| 8 | AdenoCA | G1 | |
| 9 | AdenoCA | G3A | |
| 10 | Carcinosarcoma | G3 | |
| 11 | AdenoCA | G2 | |
| 12 | AdenoCA | G2 | |
| 13 | AdenoCA | G2 | |

## Cervix

| Sample # | Diagnosis | Grade | Stage | 24P4C12 |
|---|---|---|---|---|
| 1 | Normal Cervix | | | |
| 2 | Intraepithelial neoplasia | 2-3 | T3AN0MX | |
| 3 | AdenoCA | 1 | IIA | |
| 4 | AdenoCA | 1 | IIA | |
| 5 | AdenoCA | 1 | IIA | |
| 6 | AdenoCA | 2 | IIB | |
| 7 | Non-keratinizing squamous cell | 2 | T2aNXM0 | |
| 8 | Non-keratinizing squamous cell | 2 | IIB | |
| 9 | Mucinous AdenoCA | 2 | IIB | |
| 10 | AdenoCA | 2 | T3bNXM0 | |
| 11 | Adenosquamous | 2B | T2bNXM0 | |
| 12 | AdenoCA | well diff. | III | |
| 13 | AdenoCA | mod. diff. | III | |
| 14 | Keratinizing squamous cell | 1 | | |
| 15 | Keratinizing squamous cell | 2 | T2aNXM0 | |

## Bladder

| Sample # | Pathology | Grade | 24P4C12 |
|---|---|---|---|
| 1 | Normal Bladder | | |
| 2 | Transitional | 3 | |
| 3 | Transitional | 3 | |
| 4 | Transitional | 3 | |
| 5 | Squamous | | |
| 6 | Papillary | 3 | |
| 7 | Transitional | 3 | |
| 8 | Transitional | 3 | |
| 9 | Transitional | 2 | |
| 10 | Transitional | 2 | |
| 11 | Papillary | 1 | |
| 12 | Transitional | 3 | |
| 13 | ND | | |
| 14 | Transitional | 2 | |
| 15 | Papillary | 3 | |
| 16 | Transitional | | |
| 17 | Squamous | | |
| 18 | Transitional | 3 | |
| 19 | Transitional | 3 | |

Strong expression
Medium expression
Low expression
No expression

Exhibit F

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